

Review article

Pathophysiology, mechanisms, and managements of tissue hypoxia

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ABSTRACT

Oxygen is needed to generate aerobic adenosine triphosphate and energy that is required to support vital cellular functions. Oxygen delivery (DO_2) to the tissues is determined by convective and diffusive processes. The ability of the body to adjust oxygen extraction (ERO_2) in response to changes in DO_2 is crucial to maintain constant tissue oxygen consumption (VO_2). The capability to increase ERO_2 is the result of the regulation of the circulation and the effects of the simultaneous activation of both central and local factors. The endothelium plays a crucial role in matching tissue oxygen supply to demand in situations of acute drop in tissue oxygenation. Tissue oxygenation is adequate when tissue oxygen demand is met. When DO_2 is severely compromised, a critical DO_2 value is reached below which VO_2 falls and becomes dependent on DO_2 , resulting in tissue hypoxia. The different mechanisms of tissue hypoxia are circulatory, anaemic, and hypoxic, characterised by a diminished DO_2 but preserved capacity of increasing ERO_2 . Cytopathic hypoxia is another mechanism of tissue hypoxia that is due to impairment in mitochondrial respiration that can be observed in septic conditions with normal overall DO_2 . Sepsis induces microcirculatory alterations with decreased functional capillary density, increased number of stopped-flow capillaries, and marked heterogeneity between the areas with large intercapillary distance, resulting in impairment of the tissue to extract oxygen and to satisfy the increased tissue oxygen demand, leading to the development of tissue hypoxia. Different therapeutic approaches exist to increase DO_2 and improve microcirculation, such as fluid therapy, transfusion, vasopressors, inotropes, and vasodilators. However, the effects of these agents on microcirculation are quite variable.

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List of abbreviations: DO_2 , oxygen delivery; DO_2Crit , critical value of DO_2 ; VO_2 , oxygen consumption; ERO_2 , oxygen extraction; CO, cardiac output; ATP, adenosine triphosphate; ADP, adenosine diphosphate; Pi, inorganic phosphate; DNA, deoxyribonucleic acid; Hb, haemoglobin; SaO_2 , arterial oxygen saturation; CaO_2 , arterial oxygen content; CvO_2 , venous oxygen content; PaO_2 , arterial oxygen partial pressure; PCO_2 , carbon dioxide partial pressure; 2,3-DPG, 2,3 diphosphoglycerate; iNOS, inducible nitric oxide synthase; NO, nitric oxide; NADH, nicotinic adenine dinucleotide; FADH_2 , flavine adenine dinucleotide; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid cycle; O_2^- , oxygen anion; ONOO^- , peroxynitrite; PARP-1, poly-ADP-ribosyl polymerase; LPS, lipopolysaccharide; CLP, cecal ligation and puncture; RBC, red blood cells; MAP, mean arterial pressure; RCT, randomised controlled trial; SSC, Surviving Sepsis Campaign; SVR, systemic vascular resistance; CI, confidence interval; PGI_2 , Prostaglandin I_2 .

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1. Introduction

Important cellular processes, ranging from deoxyribonucleic acid (DNA) and protein synthesis, require energy primarily obtained from the degradation of adenosine triphosphate (ATP) to form adenosine diphosphate (ADP) and inorganic phosphate (Pi) [1]. Aerobic generation of ATP occurs in the mitochondria through oxidative phosphorylation. This is a complex reaction powered by the proton gradient across the mitochondrial inner membrane, which is generated by the electron transport chain (mitochondrial respiration), in which the final electron acceptor is oxygen (Fig. 1) [2]. Therefore, a steady supply of oxygen is needed to generate the energy required to support vital cellular functions. If oxygen availability is limited or oxygen utilisation by the cell is altered, cellular oxygen consumption may fall, leading to organ dysfunction. Vital cellular functions can no longer be sustained, and irreversible impairments may develop if the situation persists. Moreover, tissue hypoxia occurs when tissue cells have abnormal oxygen utilisation, resulting in anaerobic metabolism [3].

Tissues have no storage system for oxygen. Thus, it is essential to maintain adequate oxygen supply to the cells and conserve their oxygen utilisation capacity to preserve organ function and avoid tissue hypoxia and death. We herein review the concept of oxygen delivery, the relationship between oxygen consumption and oxygen delivery, the mechanisms of tissue oxygen alterations, and different therapeutic approaches.

2. The concept of oxygen delivery

Oxygen delivery (DO_2) is determined by cardiac output (CO), haemoglobin concentration (Hb), and arterial oxygen saturation (SaO_2) [4]. DO_2 can be calculated using the following formula:

$$\text{DO}_2 = \text{CaO}_2 \times \text{CO} \times 10 = (1.34 \times \text{Hb} \times \text{SaO}_2 + (0.003 \times \text{PaO}_2)) \times \text{CO} \times 10$$

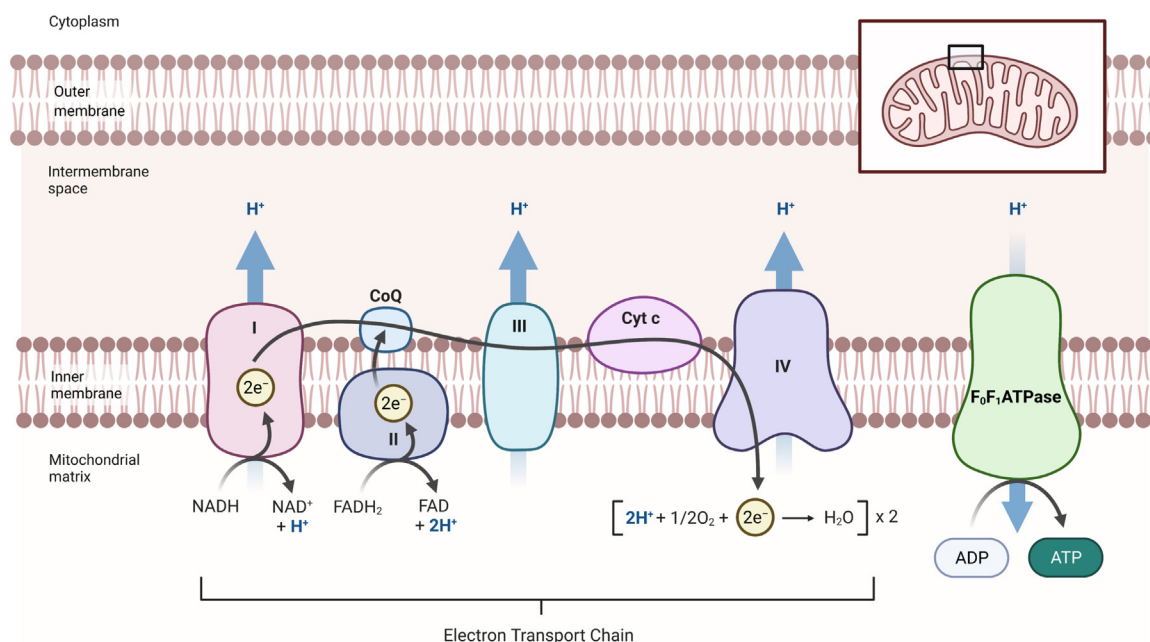


Fig. 1. Schematic representation of the mitochondrial oxidative phosphorylation. Electrons (e^-) donated from the reducing agent, nicotinae adenine dinucleotide (NADH), move progressively from Complex I through Coenzyme Q to Complex III and then through cytochrome c with oxygen (O_2) being the terminal acceptor at Complex IV. Electrons donated from another reducing agent, flavin adenine dinucleotide (FADH_2), move from Complex II to Complex III by way of Coenzyme Q. This movement of electrons results in a shift of protons (H^+) across the inner mitochondrial membrane into the intermembrane space by Complexes I, III, and IV generating the electrochemical gradient (energy) necessary for $\text{F}_0\text{F}_1\text{ATPase}$ to produce adenosine triphosphate (ATP) from adenosine diphosphate (ADP).

Where CaO_2 is the arterial oxygen content, PaO_2 is the arterial oxygen partial pressure, and 1.34 are the millilitres of oxygen bound to 1 g of Hb. CaO_2 mainly depends on SaO_2 and Hb concentration, as the amount of dissolved oxygen in the blood is minimal (0.003 mL of oxygen dissolved in 100 mL of blood for 1 mmHg of PO_2). The level of SaO_2 is determined by the oxygen-haemoglobin dissociation curve (Fig. 2). Many factors such as temperature, pH, carbon dioxide partial pressure (PCO_2), and 2,3 diphosphoglycerate (2,3-DPG) affect the Hb affinity to oxygen. These factors shift the oxygen-haemoglobin dissociation curve. A right shift of the curve as seen in situations of fever, acidosis, hypercapnia, or elevated 2,3-DPG indicates a decreased Hb affinity for oxygen, which facilitates the release of oxygen to the cells. The opposite changes in these factors induce a left shift of the oxygen-haemoglobin dissociation curve indicating an increased affinity of Hb for oxygen, but with reducing tissue oxygen availability. From the DO_2 equation, it may appear that manipulating SaO_2 and Hb levels are as effective as manipulating cardiac output (CO). However, SaO_2 usually is close to 100%, and Hb concentration cannot change acutely. Also, a decrease in SaO_2 or Hb concentration can be compensated for by an increase in CO, while the reverse is not valid [5]. Therefore, DO_2 is fundamentally dependent on CO, and SaO_2 or Hb concentration levels have a meagre contribution to DO_2 , except in situations with extreme hypoxaemia.

Diffusion is the mechanism by which oxygen is transferred from blood to tissue cells. It is dependent on the gradient in PO_2 between the capillary blood and mitochondria, and the diffusion distance between vessels to cells. Diffusion distance is determined by the capillary density and the degree of tissue oedema (Fig. 3). Mathematical models of tissue hypoxia show that the drop in cellular oxygen resulting from an increase in intercapillary distance is more severe if the decrease in tissue DO_2 is caused by a fall in PaO_2 rather than a fall in flow or Hb [6].

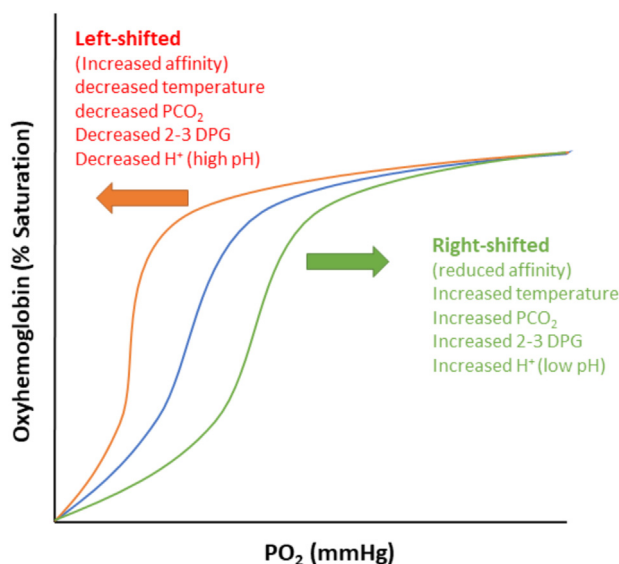


Fig. 2. Oxyhaemoglobin dissociation curve. The blue line shows the normal standard curve. Conditions that shift the curve to the right (green curve) and decrease the oxygen affinity are fever, hypercapnia, acidosis, and increased 2,3 diphosphoglycerate (2,3-DPG). Conditions that shift the curve to the left (red curve) and increase the oxygen affinity are hypothermia, hypocapnia, alkalosis, and decreased 2,3-DPG.

3. Relationship between oxygen consumption and oxygen delivery

Global oxygen consumption (VO_2) is the rate at which oxygen is taken up from the blood and consumed by the tissues. VO_2 can be derived from the CO and arterial and venous oxygen contents (CvO_2) according to the Fick equation:

$$\text{VO}_2 = \text{CO} \times (\text{CaO}_2 - \text{CvO}_2) \times 10$$

Tissue oxygenation is adequate when tissue oxygen demand is satisfied. The fundamental characterisation of the relationship between VO_2 and DO_2 came from the findings of experimental animal studies by Cain [7–9], and others [10–12]. Tissue VO_2 is determined by cellular metabolic needs, and it is independent of DO_2 over a wide range of values because compensatory adjustments occur to satisfy the oxygen requirements of peripheral tissues. When DO_2 is acutely decreased by a drop in blood flow (CO), Hb concentration, or SaO_2 levels, the oxygen extraction increases, and VO_2 can therefore be maintained stable for a long time (supply-independency). It is only when DO_2 drops below a critically low value ($\text{DO}_{2\text{crit}}$) that VO_2 starts to decrease (supply-dependency) (Fig. 4). At $\text{DO}_{2\text{crit}}$, cells shift toward anaerobic metabolism as reflected by the development of tissue metabolic acidosis.

4. Physiology of tissue oxygen extraction

The oxygen extraction ratio (ERO_2) is the proportion of arterial oxygen that is removed from the blood as it passes the microcirculation:

$$\text{ERO}_2 = \text{VO}_2 / \text{DO}_2$$

Normal ERO_2 ranges from 0.25 to 0.3 [4].

The body adjusts ERO_2 in response to changes in DO_2 through two complementary mechanisms that act to prevent the occurrence of tissue hypoxia. First, blood flow into organs is regulated by the vascular tone of the vessels, including the arteriolar system (flow-controlling vessels). These vessels are encircled by smooth muscles that can constrict or dilate in response to different stimulations [13]. Under normal conditions, blood flow to each organ is paired to current demands such that each of them gets a given fraction of whole-body DO_2 . However, when DO_2 is impaired, blood flow is redistributed to metabolically active organs due to an increase in sympathetically induced vasoconstrictor, preventing “vascular steal” of blood flow overperfusing organs with relatively low oxygen requirements [8,14,15]. Cain demonstrated that the use of alpha-blockade with phenoxybenzamine attenuated the increase in ERO_2 , indicating the importance of a strong vasoconstrictor sympathetic tone to promote oxygen tissue extraction during global tissue hypoxia in anaesthetised dogs [16,17]. Second, even if arteriolar blood flow goes to the right organs proportionally to their demands, there is no assurance that the capillary bed gets this blood according to tissue requirements. Therefore, in reference to the metabolic concept of microvascular regulation, tissues with rather elevated metabolic rates induce metabolic vasodilation that opposes the sympathetic vasoconstrictor tone, thus preventing the imbalance between cellular oxygen supply and demand. Local distribution of flow is determined downstream by precapillary (distribution vessels) sphincters in tissues. Any condition with decreased tissue PO_2 would induce a vascular dilation, increase the perfused capillary density, and restore normal tissue oxygenation [18–20]. In response to local tissue hypoxia, capillary recruitment can reduce intercapillary spaces, thus permitting tissues to extract

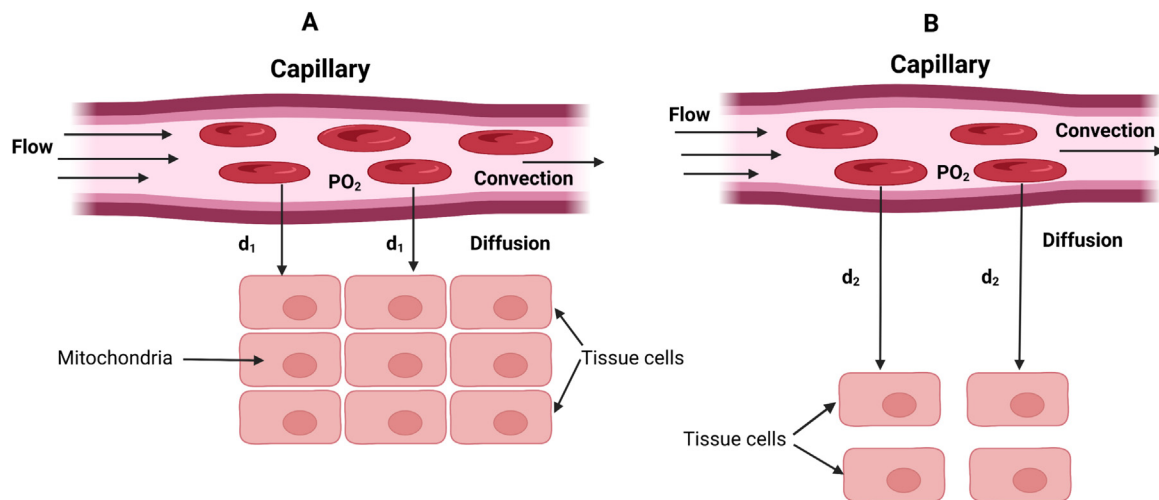


Fig. 3. Diagram showing the importance of tissue oedema in determining the capillary oxygen delivery and intracellular partial oxygen pressure (PO₂). Oxygen diffusion from capillary red blood cells (RBC) to tissue cell mitochondria is determined by the oxygen gradient from RBC to mitochondria and the diffusion distance (d₁ and d₂) from RBC to mitochondria. A, Blood flow through microcirculation under normal conditions with no tissue oedema. B, Blood flow through microcirculation under conditions with tissue oedema and increased diffusion distance [d₂] between capillary RBC and tissue cells mitochondria.

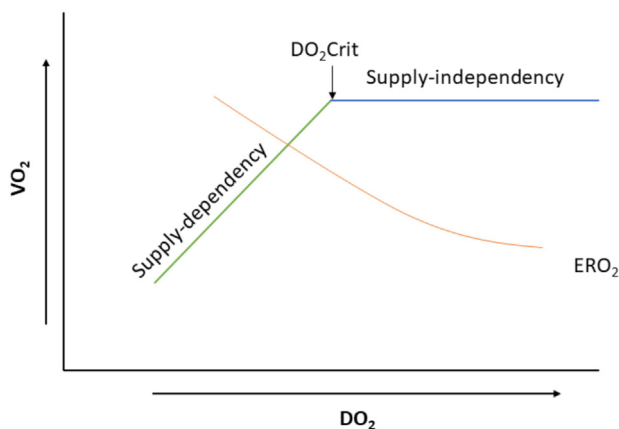


Fig. 4. Relationship between oxygen delivery (DO₂) and oxygen consumption (VO₂). When DO₂ decreases, VO₂ remains constant over a wide range of DO₂ (supply-independency, blue line) because of the increases in oxygen extraction (ERO₂, red line). When DO₂ decreases further beyond a critical value DO₂ (DO₂ Crit), VO₂ decreases along with the decreases in DO₂ (supply-dependency, green line), which defines the occurrence of tissue hypoxia and the activation of anaerobic metabolism.

oxygen effectively by reducing the capillary-to-cell diffusion distance [21].

In situations of tissue hypoxia, there is an indication that parenchymal cells generate high quantities of metabolites such as lactate, hydrogen ions, adenosine, and potassium ions that accumulate in the tissue. These cause vascular smooth muscle to relax, probably through activation of ATP-sensitive K⁺ channels, leading to increased blood flow to the hypoxic tissue [22]. However, this suggests that the cells need to experience some degree of hypoxia before the organ blood flow is changed. Consequently, other sources of control should exist. The endothelial cell is an essential element of the microvascular system. It plays a crucial function as a signal transducer of shear stress [23,24] and

vasoactive agents [25], including catecholamines, acetylcholine, prostaglandins, and others. In response to decrease in PO₂, endothelial cells release autacoid substances, including prostacyclin, nitric oxide (NO), and the endothelium-dependent hyperpolarising factor that have strong vasodilator effects on the vascular tone by stimulating soluble guanylate cyclase in vascular smooth muscle directly [26–28]. Furthermore, it has been shown that endothelial cells are implicated in tissue ERO₂ capability [29]. An endothelial oxygen detector in the vessel would allow the vasculature system to react quickly to a decline in arteriolar PO₂ without the requirement for metabolites to accumulate, with the inherent risk of hypoxia-induced cell injury. Therefore, endothelium plays a crucial role in matching tissue oxygen supply to demand in situations of acute drop in tissue oxygenation.

In summary, increased ERO₂ is the result of the regulation of the circulation and the effects of the concomitant activation of both central and local factors [8]. Central factors provoke a regional redistribution of blood flow between organs via sympathetic vasoconstrictor tone. In contrast, local factors cause an increase in the density of perfused capillaries within tissues via vasodilator tone after releasing vasodilating substances that are part of the general response termed autoregulation [30]. Altered vascular reactivity with an abnormal balance between vasoconstrictor and vasodilator tone should, therefore, fail to control blood flow distribution between and within tissues, favouring hyperperfusion of some tissue beds at the cost of hypoperfused areas, with reduced oxygen extraction capability.

5. Mechanisms of tissue hypoxia

The method by which DO₂ is altered determines the mechanism of tissue hypoxia. According to the DO₂ formula, hypoxic hypoxia (drop in SaO₂), anaemic hypoxia (drop in Hb), and circulatory hypoxia (drop in CO) are the different pathophysiological mechanisms of tissue hypoxia. It is not rare for such conditions to be concomitantly seen in critically ill patients. Another proposed mechanism to explain tissue hypoxia in situations of preserved DO₂ is cytopathic hypoxia [31].

5.1. Hypoxic, anaemic, and low flow tissue hypoxia

In normal conditions, tissue VO_2 is determined by cellular metabolic requirements and is not influenced by the quantity of oxygen delivered because of progressive increases in ERO_2 [32,33]. When DO_2 is severely compromised, a critical DO_2 is reached below which VO_2 falls and becomes dependent on DO_2 (oxygen-supply dependency), resulting in anaerobic metabolism activation [7], leading to severe acidosis and eventual cell death, if not corrected. This is due to the fact that ERO_2 does not increase proportionally to the decrease in DO_2 . This biphasic nature of DO_2 and VO_2 has been observed in normal intestinal tissue and during ischaemia. There is no one $\text{DO}_{2\text{crit}}$ value for the whole organism. Each organ has its own $\text{DO}_{2\text{crit}}$ according to its capability of oxygen extraction. Hence, tissue hypoxia is an earlier phenomenon in the skin, whereas it is delayed in the brain and heart during reductions in DO_2 .

Circulatory (hypovolaemic, cardiogenic, and obstructive types of shock), anaemic and hypoxic tissue hypoxia are characterised by a diminished DO_2 but preserved capacity of increasing ERO_2 (physiological oxygen supply dependency). In an experimental study of splenectomised dogs that were made progressively anaemic (reaching haematocrit as low as 10%) by replacement of blood with colloid (anaemic hypoxia model), and another group with progressive hypoxia (hypoxic hypoxia model) by breathing air mixed with nitrogen (reaching oxygen inspired fraction as low as 6%), Cain observed that excess lactate production appeared at about the same level of DO_2 ($\text{DO}_{2\text{crit}} = 12 \text{ mL/kg/min}$) in both models [34]. In a more detailed study with isovolumic haemodilution anaemic dogs and hypoxic hypoxia dogs, Cain observed that VO_2 was limited at a higher mixed venous PO_2 level in the anaemic model than in the hypoxic model (45 mmHg vs. 17 mmHg, respectively). However, oxygen supply dependency occurred at the same $\text{DO}_{2\text{crit}}$ level (9.8 mL/kg/min) in both models [7]. Schwartz et al. investigated the effects of haemorrhagic (hypovolaemic), normovolaemic anaemia, and hypoxia models in dogs [35]. They found that with progressively decreasing DO_2 , ERO_2 increased to the same extent in each model and continued to increase even after reaching $\text{DO}_{2\text{crit}}$ and decreased only at very low DO_2 values in the three experiments. There were differences in the haemodynamic responses to the three types of decreases in DO_2 . Indeed, CO increased in the anaemic model and greater rise in systemic and pulmonary vascular resistances in the haemorrhagic model. In that study, $\text{DO}_{2\text{crit}}$ level was also the same in the three models of tissue hypoxia around 10 mL/kg/min, and the VO_2/DO_2 dependency phenomenon (precipitous drop in VO_2) occurred only at near-death [35].

Intestinal tissue oxygenation is relatively more resilient to hypoxic hypoxia than to reduced blood flow (hypoxic ischaemia). The ability to endure pure hypoxia is dependent on preserved blood flow to intestinal tissues. Indeed, during progressive ischaemia, in intact dog intestine, VO_2 decreased when DO_2 reduced to 60% of its baseline value [36]. However, when DO_2 was compromised by pure hypoxia, VO_2 did not fall and did not become dependent on DO_2 despite a decrease to 36% of its baseline. ERO_2 increased with decreasing DO_2 but did not reach a plateau, suggesting no diffusion limitation. VO_2 stayed independent to a very low level of DO_2 because the blood flow part of DO_2 was maintained. Also, in another experimental study, VO_2 was found to be independent of DO_2 in a pure hypoxic model, in fetal lamb intestines, despite decreases in DO_2 to 43% of baseline [37]. The capacity of the intestines to keep appropriate oxygenation in the face of hypoxia might be explained in part by the strong vasodilatory effects of hypoxia in the small bowel. It has been shown that arterial hypoxia induces an increase in blood flow up to

146% of control group in intestinal small bowel [38]. In an effort to maintain adequate tissue oxygenation, ischaemic, anaemic, or hypoxic intestinal tissue will react by modulating the blood flow by acting on the local arteriolar tone [39,40] and by controlling the pre-capillary sphincters, which allows to increase the number of perfused capillaries in the surface area and decrease the capillary-to-cell diffusion distance leading to increase in ERO_2 .

5.2. Altered tissue oxygen extraction

The reduced capability of oxygen extraction has been observed in animal models of sepsis and septic patients. In a model of haemorrhagic shock with stepwise decrease in DO_2 , $\text{DO}_{2\text{crit}}$ value was high, and ERO_2 was low in the whole body of anaesthetised dogs that were challenged with either live bacteria or LPS [9,41]. This suggests that sepsis caused by bacterial infection may induce regional alterations in vascular tones. Several studies reported impairments of contractile responses to α -adrenergic agonists such as angiotensin II and serotonin in vasculature tissue from endotoxaemic animals [42–45]. It was reported that iNOS inhibitors reinstate the contractile responses of the animals' vessels to agonists [43]. These observations align with the pathophysiologic hallmarks of sepsis in clinical and experimental conditions, which is intense vasodilation with dysregulation of blood flow distribution between organs. However, in vivo endotoxaemic animal models, blocking iNOS failed to reinstate a normal ERO_2 , and to improve survival [46,47]. Furthermore, increasing α -adrenergic tones with treatments was not enough to improve ERO_2 during septic shock [48]. These results suggest that impaired vasoconstriction cannot entirely explain the altered ERO_2 observed in septic shock, and derangements in vasodilator tones should occur since a normal ERO_2 response results from an adequate balance between vasoconstrictor and vasodilator tones.

Attenuated acetyl-choline-induced dilation in vascular rings isolated from large arteries from endotoxaemic animals was reported by many studies [44]. These observations suggest impaired NO secretion by endothelial cells secondary to a defect in the expression of the constitutive NOS isoform. This was also demonstrated in the isolated small intestine arterioles after CLP of rats [49]. Moreover, the density of tissue perfused capillaries decreased, and the spatial distribution was more heterogeneous with an increase in the number of capillaries with stop-flow and large intercapillary distance in the skeletal muscles in rats that were made septic by CLP [50]. In endotoxaemic pigs, gut capillary transit-time heterogeneity significantly increased and was associated with lower critical ERO_2 than in control animals [51]. The remaining functional capillaries compensate for the reduced capillary density by delivering more oxygen to the adjacent tissue. However, augmented oxygen flow heterogeneity apparently impairs oxygen extraction by raising critical DO_2 and reducing the critical ERO_2 [52]. Reactive hyperaemia is a test used to assess an organ's maximal capacity to raise its blood flow when oxygen demand has been maximally augmented. The rise in blood flow is due to an increase in flow in the same patent capillaries and by recruiting other capillaries [53,54]. This response is due to vasoactive agents affecting the arteriole smooth muscle and those acting through the arteriole endothelium [54,55]. Using laser Doppler flowmetry, it has been shown that after stopping the leg blood flow by inflating a pneumatic cuff, the reactive hyperaemia was decreased in critically ill septic patients despite increase in DO_2 of the whole body [56]. Possible mechanisms that might explain these findings are impaired vascular reactivity to vasodilate and microvascular obstruction limiting capillary recruitment ability. Using orthogonal polarisation spectral imaging technique to assess the sublingual microcirculation, De Backer

et al. found that the density of all vessels was significantly decreased, the proportion of perfused small vessels was significantly reduced, and a more significant number of non-perfused and intermittently perfused small vessels with a marked heterogeneity between the areas in severe sepsis critically ill patients compared to volunteers patients [57]. In a mathematical model of the determinants of DO_2 and VO_2 , a rise in blood flow heterogeneity was associated with a rise in $\text{DO}_{2\text{crit}}$ with decreased ERO_2 [58].

Capillary recruitment resulting from local hypoxia can efficiently decrease intercapillary space, thus permitting more tissues oxygen extraction. Deranged ERO_2 abilities in sepsis might result from a failure to adjust capillary density according to the local oxygen supply to demand requirements.

5.3. Cytopathic tissue hypoxia

The classical mechanisms of tissue hypoxia (hypoxic hypoxia, anaemic hypoxia, and stagnant hypoxia) were insufficient to explain the reduced ATP biosynthesis and organ dysfunction in sepsis. Thus, acquired intrinsic impairment in cellular respiration was proposed as a potential mechanism that contributes to ATP production derangement despite normal (or supranormal) PO_2 values around mitochondria inside cells. This mechanism was named “cytopathic hypoxia” by Mitchell Fink [59,60].

The evidence supporting the concept of cytopathic hypoxia came from a considerable body of experimental studies in the context of sepsis with tissue PO_2 measurements [1,61–66]. For example, in a model of septic peritonitis with cecal ligation and puncture (CLP) in rats, the mean skeletal PO_2 was not different between the resuscitated septic animals and in the normal controls [1]. Also, in anaesthetised pigs that were challenged with lipopolysaccharide (LPS), the mucosal PO_2 significantly increased after restoring CO with fluid resuscitation [62]. Furthermore, the PO_2 distribution in skeletal muscle was shifted to supranormal values in patients with septic shock, whereas it was shifted to low values in cardiogenic shock patients as expected [64]. These data suggest that tissue PO_2 levels are normal/high in resuscitated septic patients. In addition, several studies demonstrated that mitochondrial function is deranged in animals with sepsis [67,68]. Indeed, the hepatocytes' VO_2 was significantly less when the hepatocytes were isolated from septic rats than from non-septic control rats [67]. Also, the amount of VO_2 was significantly lower in ileal mucosa tissue from endotoxaemic rats that was given LPS compared with control rats [68]. These findings support the concept of impaired cellular oxygen use in sepsis condition with normal/high PO_2 levels. Interestingly, the ileal mucosa VO_2 rate was preserved when LPS challenged rats were administered with aminoguanidine to block the inducible nitric oxide synthase (iNOS), suggesting that the occurrence of cytopathic hypoxia in endotoxaemic rats needs iNOS-dependent NO production.

Aerobic production of ATP happens in mitochondria through oxidative phosphorylation (Fig. 1). The reduced forms of nicotinic adenine dinucleotide (NADH) and flavine adenine dinucleotide (FADH_2) are generated during glycolysis and the tricarboxylic acid cycle (TAC) in cells are oxidised by molecular oxygen. The energy liberated by the process is used to actively pump protons from the mitochondrial matrix into the intermediate space creating an electrochemical gradient across the inner mitochondrial membrane. This gradient pushes hydrogen ions through the F_0F_1 ATPase mitochondrial enzyme that catalyses the phosphorylation of ADP to form ATP (Fig. 1).

Several different but jointly potential mechanisms might participate in the occurrence of cytopathic hypoxia in sepsis. These mechanisms include the inhibition of pyruvate dehydrogenase (PDH) by activation of PDH kinase [69–72], limiting the

delivery of pyruvate into the mitochondrial TCA leading to excess pyruvate accumulation and increased lactate production that is not related to impaired DO_2 [70]. NO-induced inactivation of cytochrome a,a_3 is another possible mechanism of sepsis-mediated cytopathic hypoxia. Sepsis is associated with increased iNOS synthesis that results in increased generation of NO. Experimental data showed that NO generated endogenously is able to cause reversible inactivation of the enzymatic activity of cytochrome a,a_3 , which is the terminal complex of the mitochondrial electron transport chain, leading to mitochondrial dysfunction [72–74]. Acute inflammatory states, including sepsis and ischemia/reperfusion, are appropriate situations where NO reacts with oxygen anion (O_2^-) to form a potent oxidising and nitrosating agent, which is peroxynitrite (ONOO^-) [75–77]. It has been shown that ONOO^- inhibits different components of the mitochondrial function, including the mitochondrial F_0F_1 ATPase that drives phosphorylation of ADP to produce ATP and the mitochondrial enzyme complexes I and II that are involved in electron transport [78] (Fig. 1). In a rat animal model, endogenous generation of ONOO^- following in vivo LPS injection resulted in mitochondrial respiration dysfunction in the rat diaphragm [79]. The most important mechanism contributing to cytopathic tissue hypoxia in sepsis is the poly-ADP-ribosyl polymerase (PARP-1), a nuclear enzyme involved in various cellular functions, including DNA repair, replication, and cellular apoptosis [80–82]. PARP-1 is activated by single-strand breaks in nuclear DNA, leading to the degradation of NAD^+ [83], and resulting in NAD^+/NADH depletion in cells. Consequently, PARP-1 activation can result in a severe derangement of oxygen utilisation by cells, leading to cytopathic hypoxia. In acute inflammation conditions, reactive oxygen species such as ONOO^- can activate PARP-1 by inducing single-strand breaks in nuclear DNA [84]. Incubation of human enterocytic cells with cytokines (tumour necrosis factor- α , interleukin-1 β , and interferon- γ) reduced VO_2 that was measured directly using an oxygen-sensitive optode by 50% [85]. Interestingly, this phenomenon was entirely reversible when cytokines were removed. Also, PARP-1 knockout mice were resistant to the lethal LPS effects [86,87]. Moreover, blocking PARP-1 using a pharmacological agent increased survival in a porcine model of lethal bacterial peritonitis [88].

6. Therapeutic approach

6.1. Fluid therapy

Fluid infusion continues to be an indispensable part of the management of all types of shock. Originally held for hypovolaemic conditions, and to some degree septic shock, cardiogenic shock also requires fluid infusion as the vasoconstrictive state leads to extravasation of fluid into the interstitium. Thus, treatment of cardiogenic shock using careful fluid administration has become a standard, even in the presence of cardiogenic pulmonary oedema [89,90].

The goal of volume expansion is to increase CO and improve tissue perfusion. This implies correcting the oxygen accessibility in the microcirculation after microcirculatory hypoperfusion in shock states [91]. Thus, this means that adequate tissue perfusion should guarantee an adequate supply of oxygen to the tissue cells.

Fluid therapy can enhance the microcirculation if administered in a timely manner and in suitable quantities. Fluids improved microvascular perfusion by increasing the proportion of perfused small vessels and small vessels density, thus reducing perfusion heterogeneity in septic patients [92,93]. Importantly, improvement in microcirculation was mainly observed when fluid was given early (within 24 h) whereas late administration (after 48 h)

did not ameliorate the microvascular perfusion [92]. Also, the microcirculatory effects of volume expansion were relatively independent of systemic effects [92,93]. Interestingly, in preload-dependent patients, organ dysfunction improved only in those who improved their microcirculation in response to fluid administration [94]. However, excessive fluid resuscitation might be harmful by inducing tissue oedema and increasing the distance between capillaries and cells, resulting in a decrease in oxygen diffusivity (Fig. 3). Several experimental and clinical studies have demonstrated the detrimental effects of aggressive fluid administration on the outcome of sepsis [95–106]. It is unknown how much fluid should be given. The latest version of the Surviving Sepsis Campaign (SSC) guidelines still recommending the administration of 30 mL/kg of intravenous crystalloid fluid to be given within the first 3 h of resuscitation in septic patients with signs of tissue hypoperfusion [107]. However, many experts have questioned this approach as a fixed dose of 30 mL/kg was based upon a low quality of evidence, and as “one size does not fit all,” initial fluid resuscitation should be individualised to each patient's needs [107–109]. Thus, fluid administration should be guided by dynamic tests (based on heart-lung interaction) [110–112], passive leg raising test [113,114], end-expiratory occlusion test [115], mini-fluid challenge techniques [116–118], or hypoperfusion parameters [119,120]. In situations of tissue hypoperfusion, fluid resuscitation should only be given to fluid responsive patients (preload-dependent) in order to avoid fluid accumulation [121].

In this regard, fluid withdrawal by administration of diuretics resulted in improved microvascular perfusion by decreasing interstitial oedema, and thus, increasing the diffusive capacity of the microcirculation by increasing its functional capillary density [122]. Multiple trials showed the feasibility of a restrictive fluid approach in the early phase of resuscitation of septic shock patients with suggestions toward benefit with fluid restriction in some studies [123–127]. However, these studies were not powered to identify differences in patient-centred outcomes. The ongoing Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial and the Conservative vs. liberal fluid therapy in septic shock (CLASSIC) trial will shed some light to this issue [128,129].

6.2. Blood transfusion

A sufficient number of RBC should reach the microcirculation in order to increase the oxygen carrying capacity of blood and improve tissue oxygenation. To obtain this, resuscitation should achieve an adequate amount of Hb-loaded red blood cells (RBC) entering the microcirculation to meet the tissue cells' metabolic requirements since Hb concentration is the main factor of oxygen availability [130]. Therefore, the idea of sufficient tissue perfusion should enclose the RBC's convection entering the microcirculation and attain an adequate density of RBC-filled capillaries to guarantee the equally important diffusion of oxygen from the RBCs to the tissue cells [13]. These two features of tissue perfusion would be more appropriately combined into one variable, which is called tissue RBC perfusion. This theory reflects the necessity of having a sufficient capillary haematocrit and functional capillary density (diffusion capacity) integrated with adequate convection or RBC flow in the microcirculation [131].

RBC transfusion improved the sublingual microcirculation by significantly increasing the proportion of perfused vessels and the functional capillary density, and by significantly decreasing the blood flow heterogeneity in haemorrhagic shock patients [132]. Interestingly, these observed effects of transfusion on microcirculation were independent of the Hb level or the systemic effects [132]. However, in septic patients, RBC transfusion improved microvascular perfusion only in those with altered capillary

perfusion at baseline [133]. In another study performed in critically ill patients, RBC transfusion improved the microvascular perfusion in patients with impaired microcirculation but had opposite effects on patients with normal microcirculation before transfusion [134]. Interestingly, RBC transfusion at both 75 g/L and 90 g/L of Hb can ameliorate or damage the microvascular perfusion, challenging the concept of arbitrary transfusion thresholds [134].

It remains a matter of debate when we should transfuse a patient. The recent transfusion guidelines in non-bleeding critically ill patients recommend adopting a restrictive transfusion approach (Hb threshold of 70 g/L) over a liberal transfusion approach (Hb threshold 90 g/L) in the majority of critically ill patients with non-bleeding anaemia, except in patients with an acute coronary syndrome where a liberal transfusion strategy (Hb threshold of 90–100 g/L) is preferred to a restrictive strategy (Hb threshold of 70 g/L) [107,135]. No recommendations were made for elderly and oncologic or haemato-oncologic critically ill patients or for those undergoing extracorporeal membrane oxygenation [135].

In critically ill bleeding patients, the recent guidelines of the European Society of Intensive Care Medicine (ESICM) suggest adopting a restrictive RBC transfusion threshold: 70 g/L vs. 90 g/L for non-massive gastrointestinal bleeding, and 75–80 g/L vs. 100 g/L for non-massive bleeding after vascular surgery [136].

In a recent meta-analysis, RBC transfusions resulted in significant increases in DO_2 , VO_2 , and venous oxygen saturation and a significant decrease in ERO_2 without effects on CO [137]. Also, recently, Fischer et al. demonstrated that an individualised RBC transfusion strategy based on a central venous oxygen saturation threshold of 70% resulted in a significantly lower transfusion rate with no differences in postoperative morbidity or 6-month mortality compared to liberal strategy in patients admitted to intensive care unit after cardiac surgery with postoperative Hb less than 90 g/L [138]. These findings suggest that the decision to transfuse in critically ill patients should not be based on a Hb level alone but also guided by oxygenation derived variables when it is possible. Today, an acceptable strategy is that RBC transfusion can be safely withheld when the Hb is > 90 g/L and should be administered when Hb is < 70 g/L. Transfusion decisions should be individualised if the Hb is between these two values [90].

6.3. Vasopressors

Vasopressors are drugs used to increase arterial blood pressure by peripheral vasoconstriction. Different vasopressor agents have been proposed. Norepinephrine is a potent α -1 receptor agonist and mild-moderate β -1 receptor agonist with minimal β -2 receptor activity [139]. Its haemodynamic effects are dominated by α -1 receptor-induced vasoconstriction and increased systemic vascular resistance (SVR), which results in increased mean arterial pressure (MAP) with minimal effects on heart rate and CO. At high doses, norepinephrine may increase CO due to β -1 receptor activation and increases in venous return mediated by rising in the mean systemic filling pressure [140]. However, like a pure vasoconstrictor, norepinephrine may decrease CO in untreated hypovolaemia cases or in patients with cardiac dysfunction owing to the potent rise in afterload. Nevertheless, many patients with cardiogenic shock can keep CO during norepinephrine treatment [141,142]. Dopamine exerts its effects in a dose-dependent manner on dopamine-1, α -1, and β -1 receptors. At lower doses, dopamine induces vasodilation through dopamine-1 receptor activity in the kidney, splanchnic, brain, and coronary circulation. At higher doses, the activity of dopamine's α receptor prevails, which leads to vasoconstriction and increased SVR. Its β -1 receptor activity can cause dose-dependent arrhythmias [139]. Epinephrine is a potent α -1 and β -1 receptors agonists with stronger β -2

receptor activity than norepinephrine (Table 1). At low doses, epinephrine activity is mainly related to its effects on β -1 receptors resulting in increased CO and heart rate with variable responses on MAP. At higher doses, epinephrine infusion leads to an increase in SVR, MAP, and CO [139]. Potential side effects of epinephrine comprise arrhythmias and impaired splanchnic circulation [143]. Phenylephrine is a pure α -1 receptor agonist with no β -1/ β -2 receptors activity that increases arterial and venous resistance. Vasopressin is a natural hormone with strong vasoconstrictive effects. Its vasoconstrictor effects are due to activation of V1a receptors on vascular smooth muscles, resulting in increased SVR and MAP [139,144]. At high doses, vasopressin has been associated with cardiac, digital, and splanchnic ischaemia [145].

The updated version of the SSC guidelines continues to recommend norepinephrine as the first-line vasopressor for septic shock, and there is enough proof to back this recommendation [107]. Norepinephrine is also the first-line vasopressor in most types of shock, including cardiogenic shock [146]. Norepinephrine improved microvascular perfusion when used to correct severe hypotension by restoring a minimal perfusion pressure to organs [147,148]. However, increasing MAP higher than 65 mmHg (75 or 85 mmHg) had variable effects on microvascular perfusion [149,150]. Interestingly, increasing MAP with norepinephrine improved microvascular perfusion only in patients with severe impairment in sublingual microcirculation, whereas it was detrimental in patients with close to normal baseline microcirculation [150]. The SSC recommends targeting a MAP of 65 mmHg during the initial resuscitation of septic shock [107]. Although the optimal MAP target in shock states has been a subject of intense research [151,152], no universally accepted value has been recognised. Thus, target values of MAP should be personalised for a given patient considering several factors, including history of chronic hypertension, and persistent signs of tissue hypoperfusion [153].

When to start norepinephrine is still a matter of debate. In the past, vasopressor was administered only when it was deemed that the patient was fluid unresponsive. However, even untreated transient hypotension can be associated with organ dysfunction [154] or increased mortality [155]. Early administration of norepinephrine during resuscitation of severely hypotensive septic shock patients increased CO through an increase in venous return by enhancing the mean systemic filling pressure, and consequently cardiac preload, and also by improving cardiac contractility [156–158]. Early initiation of norepinephrine was associated with better outcomes in septic shock patients. In a retrospective study that included 213 septic shock patients, the 28-day mortality rate was significantly higher when norepinephrine infusion was initiated ≥ 2 h after septic shock onset. Also, every 1-h delay in norepinephrine starting during the first 6 h after septic shock onset was associated with a 5.3% increase in mortality. Further-

more, the duration of hypotension and norepinephrine requirements was significantly shorter in the early norepinephrine initiation group [159]. A phase II randomised controlled trial (RCT) with 310 septic shock patients showed that early administration of norepinephrine (median 1.5 h) was significantly associated with higher shock control by 6 h [160]. In another prospective study with propensity score-based analysis, early administration of norepinephrine (within 6 h of septic shock onset) was associated with significantly lower 24-h net fluid balance and lower risk of death at day 28 with no significant increase in acute renal failure or renal replacement therapy requirements in 186 septic shock patients [161]. These results were supported by the findings of a recent meta-analysis that included 929 patients [162]. These results suggest that norepinephrine might be used as an adjunct to fluids to increase CO and MAP in hypotensive patients. However, large-scale RCTs are required to confirm these findings. Also, the optimal timing of norepinephrine initiation is yet to be determined.

Patients with more severe septic shock may require high doses of norepinephrine due to down regulation of α 1-adrenergic receptors. High dose norepinephrine may harm myocardial cells and induce oxidative stress. Thus, a second vasopressor should be added before patients develop refractory septic shock. In a meta-analysis, the use of vasopressin was related to a reduction in the need for renal replacement therapy, a tendency toward lower 90-day mortality, but more complications such as digital ischaemia [163]. The SSC guidelines suggest adding vasopressin when the dose of norepinephrine is in the range of 0.25–0.5 μ g/kg/min [107]. In cases of myocardial dysfunction, epinephrine is a reasonable alternative [107].

Other novel vasopressor drugs (selepressin and angiotensin II) have been developed recently [164–166]. Their potential indications in septic shock patients are still under investigation.

6.4. Inotropes

In septic shock patients with persistent signs of tissue hypoperfusion after adequate fluid resuscitation and MAP and myocardial dysfunction based on suspected or measured low CO and elevated cardiac filling pressure, the SSC guidelines suggest adding dobutamine to norepinephrine or using epinephrine alone [107]. However, there are no RCTs that compared dobutamine to placebo in these patients. A network meta-analysis found that the combination of dobutamine and norepinephrine had no effect on mortality when compared to no dobutamine [167]. Nevertheless, none of the included trials directly compared the association of dobutamine and norepinephrine to norepinephrine alone. Also, there was no evidence to support the superiority of the combination of dobutamine and norepinephrine over epinephrine alone in terms of mortality [167]. The ongoing ADAPT multicentre RCT (NCT04166331) will shed light on the efficacy of dobutamine

Table 1
Vasopressors and inotropes receptors potency.

Agents	α -1 receptors	β -1 receptors	β -2 receptors	Dopamine-1 receptors	Vasopressin-1a receptors
Dobutamine	+	++++	+++	0	0
Dopamine	+++	++++	++	++++	0
Epinephrine	++++	++++	+++	0	0
Milrinone	0	0	0	0	0
Levosimendan	0	0	0	0	0
Norepinephrine	++++	+++	++	0	0
Phenylephrine	++++	0	0	0	0
Vasopressin	0	0	0	0	++++

0: no significant receptor affinity; + through ++++: minimal to maximal receptor affinity.

as an adjunctive treatment in septic shock patients with septic cardiomyopathy and tissue hypoperfusion.

Levosimendan is a calcium-sensitising drug with inotropic and vasodilatory properties. In a meta-analysis of seven RCTs, no significant difference in the mortality rate between levosimendan and dobutamine was found in sepsis and septic shock patients [168]. The SSC guidelines suggest against using levosimendan in septic shock patients and cardiac dysfunction with signs of tissue hypoperfusion despite adequate fluid resuscitation and MAP [107].

In patients with cardiogenic shock, the first line inotropic agent is dobutamine [146,169,170]. Levosimendan may be used in cardiogenic shock patients already on chronic beta-blocker therapy and in patients with cardiogenic shock with acute right ventricular failure or pulmonary hypertension due to its positive effects on pulmonary vascular resistance mediated by potent phosphodiesterase-3 inhibition [146]. Milrinone, a selective phosphodiesterase-3 inhibitor, and dobutamine had similar effectiveness and safety profiles [171], but may be harmful in ischaemic decompensated heart failure [172].

6.5. Additional therapies

a) Corticosteroids

Corticosteroids enhance cardiovascular function by restoring adequate blood volume through augmented mineralocorticoid activity and by improving SVR, vascular contractile, and blood pressure responses to α_1 -agonists, an effect that is partially linked to endothelial glucocorticoid receptors [173]. A meta-analysis that included 22 RCTs and 7297 septic shock patients, low dose of corticosteroids accelerated the resolution of shock (mean difference: 1.52 days; 95% CI: 1.71–1.32), reduced duration of invasive mechanical ventilation (mean difference: 1.38 days; 95% CI: 0.8–1.96), and ICU stay (mean difference: 1.34 days; 95% CI: 0.75; 95% CI: 0.17–1.34). However, low dose corticosteroids had no effect on short- or long-term mortality. Also, the risk of experiencing any adverse event was higher with corticosteroids [174]. The overall quality of evidence was moderate. However, the experts judged that the beneficial effects outweigh the undesirable effects. Thus, the SSC guidelines suggest using low dose systemic corticosteroids in septic shock patients with ongoing requirements of vasopressor treatment [107]. It is suggested to start intravenous hydrocortisone at dose of 200 mg/day administered as 50 mg every 6 h or as a continuous infusion in septic shock patients with norepinephrine dose $\geq 0.25 \mu\text{g/kg/min}$ for at least 4 h after initiation to maintain the target MAP [107]. However, the optimal dose, timing of administration, and duration of corticosteroids remain uncertain.

b) Vitamin C/vitamin B1

Vitamin C (ascorbic acid) has pleiotropic properties, including antioxidant and anti-inflammatory effects. It acts as a cofactor in the biosynthesis of norepinephrine and vasopressin, enhances catecholamine sensitivity, and protects the microcirculation [175,176]. Potential side effects of high doses of intravenous vitamin C are oxalate nephropathy, and haemolysis in patients with glucose-6-phosphate deficiency [175]. Vitamin B1 (thiamine) is an essential cofactor in energy metabolism, and vitamin B1 deficit induces mitochondrial dysfunction and oxidative stress [175]. Vitamin C and vitamin B1 are depleted in sepsis [177,178]. Therefore, the supplementation of vitamin C and vitamin B1 has been suggested as a therapy for improving organ function in septic shock patients [179–181].

Whether vitamin C, corticosteroids, and vitamin B1 alone or in combination improve septic patients' clinical outcomes has been a topic of extensive investigation. In 2017, a single-centre retrospective before-after study found an impressive decrease in-hospital mortality (odds ratio: 0.13; 95% CI: 0.04–0.48), improved organ function, and shorter duration of vasopressor treatment in sepsis and septic shock patients who received the combination of vitamin C, vitamin B1, and hydrocortisone compared to control patients [182]. Following this study, 8 RCTs and many meta-analyses of RCTs [183–188] were published with conflicting results. All the meta-analyses showed that the combination of vitamin C, vitamin B1, and hydrocortisone had no effect on sepsis and septic shock mortality [183–188]. Also, most of the meta-analyses reported either a significant reduction in organ dysfunction (SOFA score) or shorter duration of vasopressors or both in septic patients who received these treatments than the control group [183–186,188]. However, in most of the included RCTs [189–195], the patients in the control group received placebo and a few of them received hydrocortisone as co-intervention. Therefore, these meta-analyses [183–186,188] cannot answer whether the adjunction of vitamin C or vitamin B1 to hydrocortisone is superior to hydrocortisone alone in terms of shock resolution or improvement in organs function. The recent network meta-analysis [187] did not find any evidence that the combination of vitamin C, vitamin B1, and corticosteroids results in shorter vasopressors treatment duration or reduction in organ dysfunction than corticosteroids alone [187]. However, these results should be interpreted with caution, as data for this comparison are scarce. Until further evidence from ongoing RCTs, the SSC guidelines suggest against using vitamin C in septic shock patients [107].

c) Vasodilators

Vasodilator agents can play a role in manipulating the microcirculation as the reduced vascular density and stopped-flow capillaries can be due to exaggerated vasoconstriction. The topical administration of acetylcholine, an endothelium-dependent vasodilating agent, directly on the sublingual area, restored the microvascular blood flow derangements by recruiting capillaries of the sublingual microcirculation in septic patients [57]. Also, the infusion of nitroglycerin intravenously improved the sublingual microvascular flow in a small series of fluid resuscitated septic shock patients [196]. However, these findings were not confirmed by a randomised controlled trial that included 70 severe sepsis and septic shock patients where the authors found no effects of intravenous nitroglycerin on the sublingual microcirculatory blood flow [197]. This observation may be due to the fact that the sublingual microcirculation was minimally damaged at baseline with a normal proportion of perfused capillaries, leaving no space for further improvement [197]. In patients with circulatory shock and persistent tissue hypoperfusion after 6 h of resuscitation, and macrohaemodynamic stabilisation, the nitroglycerin infusion improved the peripheral perfusion [198]. However, in a randomised trial that included 46 septic shock patients, after achieving normal macrohaemodynamic targets, inhaled NO (40 ppm) did not improve the sublingual microcirculation compared to placebo [199]. Prostaglandin I_2 (PGI_2) analogs act as a potent arteriolar vasodilator and have been used in critical limb ischaemia and frostbite to improve tissue perfusion by restoring the microcirculation. In an experimental sepsis model, iloprost, a PGI_2 -analog, improved kidney perfusion and function [200]. In a case series study of four septic shock patients with persistent signs of tissue hypoperfusion (mottling skin and increased capillary refill time) after optimising the macrocirculation, iloprost infusion resulted in improved microvascular perfusion and almost complete resolution

of hypoperfusion signs [201], suggesting promising findings. However, clinical evidence is lacking, and Iloprost is currently being investigated in a multicentre RCT (NCT03788837). Therefore, until further evidence, vasodilating agents use cannot be recommended. One of the reasons for this relative failure is the absence of selectivity of these agents, which dilate both the non-perfused and perfused vessels, resulting in unwarranted over perfusion of some areas.

7. Conclusions

Under stable conditions of oxygen requirement, VO_2 can be maintained despite a wide range of variation in DO_2 by adjusting ERO_2 with different mechanisms, including the regulation of the circulation and the endothelium effects. When DO_2 is severely compromised, a critical DO_2 value is reached below which VO_2 falls and becomes dependent on DO_2 , resulting in tissue hypoxia. The different mechanisms of tissue hypoxia are circulatory, anaemic, and hypoxic, characterised by a diminished DO_2 but preserved capacity of increasing ERO_2 . Cytopathic hypoxia is another mechanism of tissue hypoxia that is due to impairment in mitochondrial respiration that can be observed in septic conditions with normal overall DO_2 . Altered tissue oxygen extraction, caused by impaired systemic compensatory vasoconstriction and microvascular reactivity to vasodilate with limited capillary recruitment, is also reported in inflammatory situations due to the release of vasoactive substances, and can result in tissue hypoxia by an inability to satisfy increased tissue oxygen demand. Different therapeutic approaches exist to increase DO_2 , such as fluid therapy, transfusion, and inotropes. Also, there is little therapeutic ability to manipulate the other determinants of tissue hypoxia. Vasopressors, corticosteroids, vitamin C, and vasodilators were proposed to improve microcirculation. However, the effect of these agents on microcirculation and clinical outcomes are quite variable.

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JM and MOF conceived the manuscript.

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References

- [1] Astiz M, Rackow EC, Weil MH, Schumacher W. Early impairment of oxidative metabolism and energy production in severe sepsis. *Circ Shock* 1988;26(3): 311–20.
- [2] Bertram R, Gram Pedersen M, Luciani DS, Sherman A. A simplified model for mitochondrial ATP production. *J Theor Biol* 2006;243(4):575–86.
- [3] Richard C. Tissue hypoxia. How to detect, how to correct, how to prevent? *Intensive Care Med* 1996;22(11):1250–7.
- [4] Castro RH, Bakker J. Oxygen transport and tissue utilization. In: Book: Monitoring Tissue Perfusion in Shock. Springer; 2018.
- [5] Vincent JL, De Backer D. My paper 20 years later: effects of dobutamine on the VO_2/DO_2 relationship. *Intensive Care Med* 2014;40(11):1643–8.
- [6] Schumacher PT, Samsel RW. Analysis of oxygen delivery and uptake relationships in the Krogh tissue model. *J Appl Physiol* (1985) 1989;67(3):1234–44.
- [7] Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol Respir Environ Exerc Physiol* 1977;42(2):228–34.
- [8] Schumacher PT, Cain SM. The concept of a critical oxygen delivery. *Intensive Care Med* 1987;13(4):223–9.
- [9] Nelson DP, Samsel RW, Wood LD, Schumacher PT. Pathological supply dependence of systemic and intestinal O_2 uptake during endotoxemia. *J Appl Physiol* (1985) 1988;64(6):2410–9.
- [10] Van der Linden P, Gilbert E, Paques P, Simon C, Vincent JL. Influence of hematocrit on tissue O_2 extraction capabilities during acute hemorrhage. *Am J Physiol* 1993;264(6 Pt 2):H1942–7.
- [11] De Backer D, Roman A, Van der Linden P, Armistead C, Schiltz G, Vincent JL. The effects of balloon filling into the inferior vena cava on the $VO_2 DO_2$ relationship. *J Crit Care* 1992;7(3):167–73.
- [12] Zhang H, Spapen H, Benlabed M, Vincent JL. Systemic oxygen extraction can be improved during repeated episodes of cardiac tamponade. *J Crit Care* 1993;8(2):93–9.
- [13] Bateman RM, Sharpe MD, Ellis CG. Bench-to-bedside review: microvascular dysfunction in sepsis—hemodynamics, oxygen transport, and nitric oxide. *Crit Care* 2003;7(5):359–73.
- [14] Vallet B. Vascular reactivity and tissue oxygenation. *Intensive Care Med* 1998;24(1):3–11.
- [15] Schumacher PT, Samsel RW. Oxygen delivery and uptake by peripheral tissues: physiology and pathophysiology. *Crit Care Clin* 1989;5(2):255–69.
- [16] Cain SM. Effects of time and vasoconstrictor tone on O_2 extraction during hypoxic hypoxia. *J Appl Physiol Respir Environ Exerc Physiol* 1978;45(2):219–24.
- [17] Cain SM, Chapler CK. O_2 extraction by canine hindlimb during alpha-adrenergic blockade and hypoxic hypoxia. *J Appl Physiol Respir Environ Exerc Physiol* 1980;48(4):630–5.
- [18] Shepherd AP. Role of capillary recruitment in the regulation of intestinal oxygenation. *Am J Physiol* 1982;242(5):G435–41.
- [19] Lindbom L, Tuma RF, Arfors KE. Influence of oxygen on perfused capillary density and capillary red cell velocity in rabbit skeletal muscle. *Microvasc Res* 1980;19(2):197–208.
- [20] Duling BR, Klitzman B. Local control of microvascular function: role in tissue oxygen supply. *Annu Rev Physiol* 1980;42:373–82.
- [21] Grum CM. Tissue oxygenation in low flow states and during hypoxemia. *Crit Care Med* 1993;21(2 Suppl):S44–9.
- [22] Nakhostine N, Lamontagne D. Adenosine contributes to hypoxia-induced vasodilation through ATP-sensitive K^+ channel activation. *Am J Physiol* 1993;265(4 Pt 2):H1289–93.
- [23] Griffith TM. Endothelial control of vascular tone by nitric oxide and gap junctions: a haemodynamic perspective. *Biorheology* 2002;39(3–4):307–18.
- [24] Fisher AB, Chien S, Barakat AI, Nerem RM. Endothelial cellular response to altered shear stress. *Am J Physiol Lung Cell Mol Physiol* 2001;281(3):L529–33.
- [25] Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;288(5789):373–6.
- [26] Pohl U, Busse R. Hypoxia stimulates release of endothelium-derived relaxant factor. *Am J Physiol* 1989;256(6 Pt 2):H1595–600.
- [27] Michiels C, Arnould T, Knott I, Dieu M, Remacle J. Stimulation of prostaglandin synthesis by human endothelial cells exposed to hypoxia. *Am J Physiol* 1993;264(4 Pt 1):C866–74.
- [28] Mantelli L, Amerini S, Ledda F. Roles of nitric oxide and endothelium-derived hyperpolarizing factor in vasorelaxant effect of acetylcholine as influenced by aging and hypertension. *J Cardiovasc Pharmacol* 1995;25(4):595–602.
- [29] Curtis SE, Vallet B, Winn MJ, Caufield JB, King CE, Chapler CK, et al. Role of the vascular endothelium in O_2 extraction during progressive ischemia in canine skeletal muscle. *J Appl Physiol* (1985) 1995;79(4):1351–60.
- [30] Jones CJ, Kuo L, Davis MJ, Chilian WM. Regulation of coronary blood flow: coordination of heterogeneous control mechanisms in vascular microdomains. *Cardiovasc Res* 1995;29(5):585–96.
- [31] Fink MP. Cytopathic hypoxia: Is oxygen use impaired in sepsis as a result of an acquired intrinsic derangement in cellular respiration? *Crit Care Clin* 2002;18(1):165–75.
- [32] Cain SM. Peripheral oxygen uptake and delivery in health and disease. *Clin Chest Med* 1983;4(2):139–48.
- [33] Gutierrez G. The relationship of tissue oxygenation to cellular bioenergetics. *Adv Exp Med Biol* 1988;227:183–205.

- [34] Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. *Am J Physiol* 1965;209(3):604–10.
- [35] Schwartz S, Frantz RA, Shoemaker WC. Sequential hemodynamic and oxygen transport responses in hypovolemia, anemia, and hypoxia. *Am J Physiol* 1981;241(6):H864–71.
- [36] Grum CM, Fiddian-Green RG, Pittenger GL, Grant BJ, Rothman ED, Dantzer DR. Adequacy of tissue oxygenation in intact dog intestine. *J Appl Physiol Respir Environ Exerc Physiol* 1984;56(4):1065–9.
- [37] Edelstone DI, Holzman IR. Fetal intestinal oxygen consumption at various levels of oxygenation. *Am J Physiol* 1982;242(1):H50–4.
- [38] Shepherd AP. Intestinal O₂ consumption and 86Rb extraction during arterial hypoxia. *Am J Physiol* 1978;234(3):E248–51.
- [39] Granger HJ, Nyhof RA. Dynamics of intestinal oxygenation: interactions between oxygen supply and uptake. *Am J Physiol* 1982;243(2):G91–6.
- [40] Granger HJ, Shepherd Jr AP. Intrinsic microvascular control of tissue oxygen delivery. *Microvasc Res* 1973;5(1):49–72.
- [41] Nelson DP, Beyer C, Samsel RW, Wood LD, Schumacker PT. Pathological supply dependence of O₂ uptake during bacteremia in dogs. *J Appl Physiol* (1985) 1987;63(4):1487–92.
- [42] Wakabayashi I, Hatake K, Kakishita E, Nagai K. Diminution of contractile response of the aorta from endotoxin-injected rats. *Eur J Pharmacol* 1987;141(1):117–22.
- [43] Julou-Schaeffer G, Gray GA, Fleming I, Schott C, Parratt JR, Stoclet JC. Loss of vascular responsiveness induced by endotoxin involves L-arginine pathway. *Am J Physiol* 1990;259(4 Pt 2):H1038–43.
- [44] Parker JL, Keller RS, DeFily DV, Laughlin MH, Novotny MJ, Adams HR. Coronary vascular smooth muscle function in E. coli endotoxemia in dogs. *Am J Physiol* 1991;260(3 Pt 2):H832–41.
- [45] Umans JG, Wylam ME, Samsel RW, Edwards J, Schumacker PT. Effects of endotoxin in vivo on endothelial and smooth-muscle function in rabbit and rat aorta. *Am Rev Respir Dis* 1993;148(6 Pt 1):1638–45.
- [46] Schumacker PT, Kazagliis J, Connolly HV, Samsel RW, O'Connor MF, Umans JG. Systemic and gut O₂ extraction during endotoxemia. Role of nitric oxide synthesis. *Am J Respir Crit Care Med* 1995;151(1):107–15.
- [47] Cobb JP, Natanson C, Quezado ZM, Hoffman WD, Koev CA, Banks S, et al. Differential hemodynamic effects of L-NMMA in endotoxemic and normal dogs. *Am J Physiol* 1995;268(4 Pt 2):H1634–42.
- [48] Zhang H, De Jongh R, De Backer D, Cherkaoui S, Vray B, Vincent JL. Effects of alpha- and beta-adrenergic stimulation on hepatosplanchnic perfusion and oxygen extraction in endotoxic shock. *Crit Care Med* 2001;29(3):581–8.
- [49] Wang P, Ba ZF, Chaudry IH. Endothelium-dependent relaxation is depressed at the macro- and microcirculatory levels during sepsis. *Am J Physiol* 1995;269(5 Pt 2):R988–94.
- [50] Lam C, Tyml K, Martin C, Sibbald W. Microvascular perfusion is impaired in a rat model of normotensive sepsis. *J Clin Invest* 1994;94(5):2077–83.
- [51] Humer MF, Phang PT, Friesen BP, Allard F, Goddard CM, Walley KR. Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxemic pigs. *J Appl Physiol* (1985) 1996;81(2):895–904.
- [52] Ellis CG, Bateman RM, Sharpe MD, Sibbald WJ, Gill R. Effect of a maldistribution of microvascular blood flow on capillary O₂ extraction in sepsis. *Am J Physiol Heart Circ Physiol* 2002;282(1):H156–64.
- [53] Burton KS, Johnson PC. Reactive hyperemia in individual capillaries of skeletal muscle. *Am J Physiol* 1972;223(3):517–24.
- [54] Ward ME, Magder SA, Hussain SN. Role of endothelium-derived relaxing factor in reactive hyperemia in canine diaphragm. *J Appl Physiol* (1985) 1993;74(4):1606–12.
- [55] Koller A, Kaley G. Role of endothelium in reactive dilation of skeletal muscle arterioles. *Am J Physiol* 1990;259(5 Pt 2):H1313–6.
- [56] Nevriere R, Mathieu D, Chagnon JL, Lebleu N, Millien JP, Wattel F. Skeletal muscle microvascular blood flow and oxygen transport in patients with severe sepsis. *Am J Respir Crit Care Med* 1996;153(1):191–5.
- [57] De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med* 2002;166(1):98–104.
- [58] Walley KR. Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: theory. *J Appl Physiol* (1985) 1996;81(2):885–94.
- [59] Fink M. Cytopathic hypoxia in sepsis. *Acta Anaesthesiol Scand Suppl* 1997;110:87–95.
- [60] Fink MP. Cytopathic hypoxia. Mitochondrial dysfunction as mechanism contributing to organ dysfunction in sepsis. *Crit Care Clin* 2001;17(1):219–37.
- [61] Hotchkiss RS, Rust RS, Dence CS, Wasserman TH, Song SK, Hwang DR, et al. Evaluation of the role of cellular hypoxia in sepsis by the hypoxic marker [18F]fluoromisonidazole. *Am J Physiol* 1991;261(4 Pt 2):R965–72.
- [62] VanderMeer TJ, Wang H, Fink MP. Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. *Crit Care Med* 1995;23(7):1217–26.
- [63] Rosser DM, Stidwill RP, Jacobson D, Singer M. Oxygen tension in the bladder epithelium rises in both high and low cardiac output endotoxemic sepsis. *J Appl Physiol* (1985) 1995;79(6):1878–82.
- [64] Boekstegers P, Weidenhöfer S, Pilz G, Werdan K. Peripheral oxygen availability within skeletal muscle in sepsis and septic shock: comparison to limited infection and cardiogenic shock. *Infection* 1991;19(5):317–23.
- [65] Sair M, Etherington PJ, Peter Winlove C, Evans TW. Tissue oxygenation and perfusion in patients with systemic sepsis. *Crit Care Med* 2001;29(7):1343–9.
- [66] Vallet B, Lund N, Curtis SE, Kelly D, Cain SM. Gut and muscle tissue PO₂ in endotoxemic dogs during shock and resuscitation. *J Appl Physiol* (1985) 1994;76(2):793–800.
- [67] Kantrow SP, Taylor DE, Carraway MS, Piantadosi CA. Oxidative metabolism in rat hepatocytes and mitochondria during sepsis. *Arch Biochem Biophys* 1997;345(2):278–88.
- [68] King CJ, Tytgat S, Delude RL, Fink MP. Ileal mucosal oxygen consumption is decreased in endotoxemic rats but is restored toward normal by treatment with aminoguanidine. *Crit Care Med* 1999;27(11):2518–24.
- [69] Vary TC, Siegel JH, Nakatani T, Sato T, Aoyama H. Effect of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. *Am J Physiol* 1986;250(6 Pt 1):E634–40.
- [70] Vary TC. Sepsis-induced alterations in pyruvate dehydrogenase complex activity in rat skeletal muscle: effects on plasma lactate. *Shock* 1996;6(2):89–94.
- [71] Vary TC, Hazen S. Sepsis alters pyruvate dehydrogenase kinase activity in skeletal muscle. *Mol Cell Biochem* 1999;198(1–2):113–8.
- [72] Giuffrè A, Sarti P, D'Itri E, Buse G, Soulimane T, Brunori M. On the mechanism of inhibition of cytochrome c oxidase by nitric oxide. *J Biol Chem* 1996;271(52):33404–8.
- [73] Torres J, Darley-Usmar V, Wilson MT. Inhibition of cytochrome c oxidase in turnover by nitric oxide: mechanism and implications for control of respiration. *Biochem J* 1995;312(Pt 1):169–73.
- [74] Brown GC, Bolaños JP, Heales SJ, Clark JB. Nitric oxide produced by activated astrocytes rapidly and reversibly inhibits cellular respiration. *Neurosci Lett* 1995;193(3):201–4.
- [75] Wink DA, Mitchell JB. Chemical biology of nitric oxide: Insights into regulatory, cytotoxic, and cytoprotective mechanisms of nitric oxide. *Free Radic Biol Med* 1998;25(4–5):434–56.
- [76] Lu M, Wang WH. Reaction of nitric oxide with superoxide inhibits basolateral K⁺ channels in the rat CCD. *Am J Physiol* 1998;275(1):C309–16.
- [77] Radi R, Peluffo G, Alvarez MN, Naviliat M, Cayota A. Unraveling peroxynitrite formation in biological systems. *Free Radic Biol Med* 2001;30(5):463–88.
- [78] Rubbo H, Denicola A, Radi R. Peroxynitrite inactivates thiol-containing enzymes of Trypanosoma cruzi energetic metabolism and inhibits cell respiration. *Arch Biochem Biophys* 1994;308(1):96–102.
- [79] Boczkowski J, Lisdero CL, Lanone S, Samb A, Carreras MC, Boveris A, et al. Endogenous peroxynitrite mediates mitochondrial dysfunction in rat diaphragm during endotoxemia. *FASEB J* 1999;13(12):1637–46.
- [80] Durkacz BW, Omidiji O, Gray DA, Shall S. (ADP-ribose)n participates in DNA excision repair. *Nature* 1980;283(5747):593–6.
- [81] Satoh MS, Poirier GG, Lindahl T. Dual function for poly(ADP-ribose) synthesis in response to DNA strand breakage. *Biochemistry* 1994;33(23):7099–106.
- [82] Simbulan-Rosenthal CM, Rosenthal DS, Iyer S, Boulares H, Smulson ME. Involvement of PARP and poly(ADP-ribosylation) in the early stages of apoptosis and DNA replication. *Mol Cell Biochem* 1999;193(1–2):137–48.
- [83] D'Amours D, Desnoyers S, D'Silva I, Poirier GG. Poly(ADP-ribosylation) reactions in the regulation of nuclear functions. *Biochem J* 1999;342(Pt 2):249–68.
- [84] Fink MP. Bench-to-bedside review: cytopathic hypoxia. *Crit Care* 2002;6(6):491–9.
- [85] Khan AU, Delude RL, Han YY, Sappington PL, Han X, Carcillo JA, et al. Liposomal NAD(+) prevents diminished O₂ consumption by immunostimulated Caco-2 cells. *Am J Physiol Lung Cell Mol Physiol* 2002;282(5):L1082–91.
- [86] Kühnle S, Nicotera P, Wendel A, Leist M. Prevention of endotoxin-induced lethality, but not of liver apoptosis in poly(ADP-ribose) polymerase-deficient mice. *Biochem Biophys Res Commun* 1999;263(2):433–8.
- [87] Oliver FJ, Ménessier-de Murcia J, Nacci C, Decker P, Andriantsitohaina R, Muller S, et al. Resistance to endotoxic shock as a consequence of defective NF-kappaB activation in poly (ADP-ribose) polymerase-1 deficient mice. *EMBO J* 1999;18(16):4446–54.
- [88] Goldfarb RD, Marton A, Szabó E, Virág L, Salzman AL, Glock D, et al. Protective effect of a novel, potent inhibitor of poly(adenosine 5'-diphosphate-ribose) synthetase in a porcine model of severe bacterial sepsis. *Crit Care Med* 2002;30(5):974–80.
- [89] Figueras J, Weil MH. Hypovolemia and hypotension complicating management of acute cardiogenic pulmonary edema. *Am J Cardiol* 1979;44(7):1349–55.
- [90] Vincent JL, Joosten A, Saugel B. Hemodynamic monitoring and support. *Crit Care Med* 2021;49(10):1638–50.
- [91] Cecconi M, Hernandez G, Dunser M, Antonelli M, Baker T, Bakker J, et al. Fluid administration for acute circulatory dysfunction using basic monitoring: narrative review and expert panel recommendations from an ESICM task force. *Intensive Care Med* 2019;45(1):21–32.
- [92] Ospina-Tascon G, Neves AP, Occhipinti G, Donadello K, Büchele G, Simion D, et al. Effects of fluids on microvascular perfusion in patients with severe sepsis. *Intensive Care Med* 2010;36(6):949–55.
- [93] Pottecher J, Derudder S, Teboul JL, Georger JF, Laplace C, Benhamou D, et al. Both passive leg raising and intravascular volume expansion improve sublingual microcirculatory perfusion in severe sepsis and septic shock patients. *Intensive Care Med* 2010;36(11):1867–74.
- [94] Pranskunas A, Koopmans M, Koetsier PM, Pilvinis V, Boerma EC. Microcirculatory blood flow as a tool to select ICU patients eligible for fluid therapy. *Intensive Care Med* 2013;39(4):612–9.

- [95] Brandt S, Regueira T, Bracht H, Porta F, Djafarzadeh S, Takala J, et al. Effect of fluid resuscitation on mortality and organ function in experimental sepsis models. *Crit Care* 2009;13(6):R186.
- [96] Rehberg S, Yamamoto Y, Sousse L, Bartha E, Jonkam C, Hasselbach AK, et al. Selective V(1a) agonism attenuates vascular dysfunction and fluid accumulation in ovine severe sepsis. *Am J Physiol Heart Circ Physiol* 2012;303(10):H1245–54.
- [97] Rosenberg AL, Dechert RE, Park PK, Bartlett RH. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med* 2009;24(1):35–46.
- [98] Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34(2):344–53.
- [99] Alsous F, Khamiees M, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA. Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. *Chest* 2000;117(6):1749–54.
- [100] Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009;136(1):102–9.
- [101] Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008;12(3):R74.
- [102] Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009;76(4):422–7.
- [103] Micek ST, McEvoy C, McKenzie M, Hampton N, Doherty JA, Kollef MH. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. *Crit Care* 2013;17(5):R246.
- [104] Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011;39(2):259–65.
- [105] Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. *Crit Care* 2015;19(1):251.
- [106] van Mourik N, Geerts BF, Binnekade JM, Veelo DP, Bos LDJ, Wiersinga WJ, et al. A higher fluid balance in the days after septic shock reversal is associated with increased mortality: an observational cohort study. *Crit Care Explor* 2020;2(10):e0219.
- [107] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021;47(11):1181–247.
- [108] Marik PE, Byrne L, van Haren F. Fluid resuscitation in sepsis: the great 30 mL per kg hoax. *J Thorac Dis* 2020;12(Suppl 1):S37–47.
- [109] Marik PE, Malbrain M. The SEP-1 quality mandate may be harmful: How to drown a patient with 30 mL per kg fluid! *Anaesthesiol Intensive Ther* 2017;49(5):323–8.
- [110] Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000;162(1):134–8.
- [111] Myatra SN, Prabhu NR, Divatia JV, Monnet X, Kulkarni AP, Teboul JL. The changes in pulse pressure variation or stroke volume variation after a "tidal volume challenge" reliably predict fluid responsiveness during low tidal volume ventilation. *Crit Care Med* 2017;45(3):415–21.
- [112] Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Crit Care* 2014;18(6):650.
- [113] Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. *Intensive Care Med* 2016;42(12):1935–47.
- [114] Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid! *Crit Care* 2015;19(1):18.
- [115] Gavelli F, Shi R, Teboul JL, Azzolina D, Monnet X. The end-expiratory occlusion test for detecting preload responsiveness: a systematic review and meta-analysis. *Ann Intensive Care* 2020;10(1):65.
- [116] Biais M, de Courson H, Lanchon R, Pereira B, Bardonneau G, Griton M, et al. Mini-fluid challenge of 100 mL of crystalloid predicts fluid responsiveness in the operating room. *Anesthesiology* 2017;127(3):450–6.
- [117] Muller L, Toumi M, Bousquet PJ, Riu-Poulenc B, Louart G, Candela D, et al. An increase in aortic blood flow after an infusion of 100 mL colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology* 2011;115(3):541–7.
- [118] Mallat J, Meddour M, Durville E, Lemyze M, Pepy F, Temime J, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth* 2015;115(3):449–56.
- [119] Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK Randomized Clinical Trial. *Jama* 2019;321(7):654–64.
- [120] Zampieri FG, Damiani LP, Bakker J, Ospina-Tascón GA, Castro R, Cavalcanti AB, et al. Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock. A Bayesian reanalysis of the ANDROMEDA-Shock Trial. *Am J Respir Crit Care Med* 2020;201(4):423–9.
- [121] Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2014;40(12):1795–815.
- [122] Uz Z, Ince C, Guerci P, Ince Y, Araujo RP, Ergin B, et al. Recruitment of sublingual microcirculation using handheld incident dark field imaging as a routine measurement tool during the postoperative de-escalation phase—a pilot study in post ICU cardiac surgery patients. *Perioper Med (Lond)* 2018;7:18.
- [123] Chen C, Kollef MH. Targeted fluid minimization following initial resuscitation in septic shock: a pilot study. *Chest* 2015;148(6):1462–9.
- [124] Corl KA, Prodomou M, Merchant RC, Gareen I, Marks S, Banerjee D, et al. The restrictive IV fluid trial in severe sepsis and septic shock (RIFTS): a randomized pilot study. *Crit Care Med* 2019;47(7):951–9.
- [125] Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettilä V, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med* 2016;42(11):1695–705.
- [126] Macdonald SPJ, Keijzers G, Taylor DM, Kinnear F, Arendts G, Fatovich DM, et al. Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial. *Intensive Care Med* 2018;44(12):2070–8.
- [127] Semler MW, Janz DR, Casey JD, Self WH, Rice TW. Conservative fluid management after sepsis resuscitation: a pilot randomized trial. *J Intensive Care Med* 2020;35(12):1374–82.
- [128] Meyhoff TS, Hjortrup PB, Møller MH, Wetterslev J, Lange T, Kjaer MN, et al. Conservative vs liberal fluid therapy in septic shock (CLASSIC) trial—protocol and statistical analysis plan. *Acta Anaesthesiol Scand* 2019;63(9):1262–71.
- [129] Self WH, Semler MW, Bellomo R, Brown SM, de Boisblanc BP, Exline MC, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: rationale for a randomized trial. *Ann Emerg Med* 2018;72(4):457–66.
- [130] Siam J, Kadan M, Flaishon R, Barnea O. Blood flow versus hematocrit in optimization of oxygen transfer to tissue during fluid resuscitation. *Cardiovasc Eng Technol* 2015;6(4):474–84.
- [131] Ince C, De Backer D, Mayeux PR. Microvascular dysfunction in the critically ill. *Crit Care Clin* 2020;36(2):323–31.
- [132] Tanaka S, Escudier E, Hamada S, Harrois A, Leblanc PE, Vicaute E, et al. Effect of RBC transfusion on sublingual microcirculation in hemorrhagic shock patients: a pilot study. *Crit Care Med* 2017;45(2):e154–60.
- [133] Sakr Y, Chierego M, Piagnerelli M, Verdant C, Dubois MJ, Koch M, et al. Microvascular response to red blood cell transfusion in patients with severe sepsis. *Crit Care Med* 2007;35(7):1639–44.
- [134] Scheuzyer J, Zehnder A, Meier V, Yeginsoy D, Flükiger J, Siegemund M. Sublingual microcirculation does not reflect red blood cell transfusion thresholds in the intensive care unit—a prospective observational study in the intensive care unit. *Crit Care* 2020;24(1):18.
- [135] Vlaar AP, Oczkowski S, de Bruin S, Wijnberge M, Antonelli M, Aubron C, et al. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med* 2020;46(4):673–96.
- [136] Vlaar APJ, Dionne JC, de Bruin S, Wijnberge M, Raasveldt SJ, van Baarle F, et al. Transfusion strategies in bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med* 2021;47(12):1368–92.
- [137] Cavalcante Dos Santos E, Orbegozo D, Mongkolpun W, Galfo V, Nan W, Gouveia Bogossian E, et al. Systematic review and meta-analysis of effects of transfusion on hemodynamic and oxygenation variables. *Crit Care Med* 2020;48(2):241–8.
- [138] Fischer MO, Guinot PG, Debreczi S, Huette P, Beyls C, Babatasi G, et al. Individualised or liberal red blood cell transfusion after cardiac surgery: a randomised controlled trial. *Br J Anaesth* 2022;128(1):37–44.
- [139] Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. *J Cardiovasc Pharmacol Ther* 2015;20(3):249–60.
- [140] Persichini R, Silva S, Teboul JL, Jozwiak M, Chemla D, Richard C, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. *Crit Care Med* 2012;40(12):3146–53.
- [141] Rokytá Jr R, Tesařová J, Pechman V, Gajdos P, Kroužeký A. The effects of short-term norepinephrine up-titration on hemodynamics in cardiogenic shock. *Physiol Res* 2010;59(3):373–8.
- [142] Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR. Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. *Crit Care Med* 2013;41(1):143–50.
- [143] De Backer D, Creteur J, Silva E, Vincent JL. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit Care Med* 2003;31(6):1659–67.
- [144] Demiselle J, Fage N, Radermacher P, Asfar P. Vasopressin and its analogues in shock states: a review. *Ann Intensive Care* 2020;10(1):9.
- [145] Dünser MW, Mayr AJ, Tür A, Pajk W, Barbara F, Knotzer H, et al. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. *Crit Care Med* 2003;31(5):1394–8.
- [146] Chioncel O, Parissis O, Mebazaa A, Thiele H, Desch S, Bauersachs J, et al. Epidemiology, pathophysiology and contemporary management of cardio-

- genic shock – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;22(8):1315–41.
- [147] Nakajima Y, Baudry N, Duranteau J, Vicaut E. Effects of vasopressin, norepinephrine, and L-arginine on intestinal microcirculation in endotoxemia. *Crit Care Med* 2006;34(6):1752–7.
- [148] Georger JF, Hamzaoui O, Chaari A, Maizel J, Richard C, Teboul JL. Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients. *Intensive Care Med* 2010;36(11):1882–9.
- [149] Thooft A, Favory R, Salgado DR, Taccone FS, Donadello K, De Backer D, et al. Effects of changes in arterial pressure on organ perfusion during septic shock. *Crit Care* 2011;15(5):R222.
- [150] Dubin A, Pozo MO, Casabella CA, Pálizas Jr F, Murias G, Moseinco MC, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. *Crit Care* 2009;13(3):R92.
- [151] Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014;370(17):1583–93.
- [152] Lamontagne F, Richards-Belle A, Thomas K, Harrison DA, Sadique MZ, Grieve RD, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. *Jama* 2020;323(10):938–49.
- [153] Saugel B, Vincent JL, Wagner JY. Personalized hemodynamic management. *Curr Opin Crit Care* 2017;23(4):334–41.
- [154] Panwar R, Tarvade S, Lanyon N, Saxena M, Bush D, Hardie M, et al. Relative hypotension and adverse kidney-related outcomes among critically ill patients with shock. A multicenter, prospective cohort study. *Am J Respir Crit Care Med* 2020;202(10):1407–18.
- [155] Vincent JL, Nielsen ND, Shapiro NI, Gerbasi ME, Grossman A, Doroff R, et al. Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database. *Ann Intensive Care* 2018;8(1):107.
- [156] Hamzaoui O, Georger JF, Monnet X, Ksouri H, Maizel J, Richard C, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. *Crit Care* 2010;14(4):R142.
- [157] Adda I, Lai C, Teboul JL, Guerin L, Gavelli F, Monnet X. Norepinephrine potentiates the efficacy of volume expansion on mean systemic pressure in septic shock. *Crit Care* 2021;25(1):302.
- [158] Hamzaoui O, Jozwiak M, Geffriaud T, Sztymf B, Prat D, Jacobs F, et al. Norepinephrine exerts an inotropic effect during the early phase of human septic shock. *Br J Anaesth* 2018;120(3):517–24.
- [159] Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K, et al. Early versus delayed administration of norepinephrine in patients with septic shock. *Crit Care* 2014;18(5):532.
- [160] Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early use of norepinephrine in septic shock resuscitation (CEN-SER). A randomized trial. *Am J Respir Crit Care Med* 2019;199(9):1097–105.
- [161] Ospina-Tascón GA, Hernandez G, Alvarez I, Calderón-Tapia LE, Manzano-Núñez R, Sánchez-Ortiz AI, et al. Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis. *Crit Care* 2020;24(1):52.
- [162] Li Y, Li H, Zhang D. Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis. *Crit Care* 2020;24(1):488.
- [163] Nagendran M, Russell JA, Walley KR, Brett SJ, Perkins GD, Hajjar L, et al. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. *Intensive Care Med* 2019;45(6):844–55.
- [164] Russell JA, Vincent JL, Kjolbye AL, Olsson H, Blemings A, Spapen H, et al. Selepressin, a novel selective vasopressin V(1A) agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients. *Crit Care* 2017;21(1):213.
- [165] Laterre PF, Berry SM, Blemings A, Carlsen JE, François B, Graves T, et al. Effect of selepressin vs placebo on ventilator- and vasopressor-free days in patients with septic shock: the SEPSIS-ACT randomized clinical trial. *Jama* 2019;322(15):1476–85.
- [166] Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017;377(5):419–30.
- [167] Belletti A, Benedetto U, Biondi-Zoccai G, Leggieri C, Silvani P, Angelini GD, et al. The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. *J Crit Care* 2017;37:91–8.
- [168] Bhattacharjee S, Soni KD, Maitra S, Baidya DK. Levosimendan does not provide mortality benefit over dobutamine in adult patients with septic shock: a meta-analysis of randomized controlled trials. *J Clin Anesth* 2017;39:67–72.
- [169] Mebazaa A, Tolppanen H, Mueller C, Lassus J, DiSomma S, Baksyte G, et al. Acute heart failure and cardiogenic shock: a multidisciplinary practical guidance. *Intensive Care Med* 2016;42(2):147–63.
- [170] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for The diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;18(8):891–975.
- [171] Lewis TC, Aberle C, Altschuler D, Piper GL, Papadopoulos J. Comparative effectiveness and safety between milrinone or dobutamine as initial inotrope therapy in cardiogenic shock. *J Cardiovasc Pharmacol Ther* 2019;24(2):130–8.
- [172] Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003;41(6):997–1003.
- [173] Annane D. The role of ACTH and corticosteroids for sepsis and septic shock: an update. *Front Endocrinol (Lausanne)* 2016;7:70.
- [174] Rygård SL, Butler E, Granholm A, Möller MH, Cohen J, Finfer S, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2018;44(7):1003–16.
- [175] Spoelstra-de Man AME, Elbers PWG, Oudemans-Van Straaten HM. Vitamin C: should we supplement? *Curr Opin Crit Care* 2018;24(4):248–55.
- [176] Rozemeijer S, van der Horst FAL, de Man AME. Measuring vitamin C in critically ill patients: clinical importance and practical difficulties—is it time for a surrogate marker? *Crit Care* 2021;25(1):310.
- [177] Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. *Crit Care* 2017;21(1):300.
- [178] Donnino MW, Carney E, Cocchi MN, Barbash I, Chase M, Joyce N, et al. Thiamine deficiency in critically ill patients with sepsis. *J Crit Care* 2010;25(4):576–81.
- [179] Donnino MW, Andersen LW, Chase M, Berg KM, Tidswell M, Giberson T, et al. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. *Crit Care Med* 2016;44(2):360–7.
- [180] Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! *J Thorac Dis* 2016;8(6):1062–6.
- [181] Fowler 3rd AA, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med* 2014;12:32.
- [182] Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest* 2017;151(6):1229–38.
- [183] Zayed Y, Alzghoul BN, Banifadel M, Venigandla H, Hyde R, Sutcu S, et al. Vitamin C, thiamine, and hydrocortisone in the treatment of sepsis: a meta-analysis and trial sequential analysis of randomized controlled trials. *J Intensive Care Med* 2021. 885066620987809.
- [184] Assouline B, Faivre A, Verissimo T, Sangla F, Berchtold L, Giraud R, et al. Thiamine, ascorbic acid, and hydrocortisone as a metabolic resuscitation cocktail in sepsis: a meta-analysis of randomized controlled trials with trial sequential analysis. *Crit Care Med* 2021;49(12):2112–20.
- [185] Wu T, Hu C, Huang W, Xu Q, Hu B, Li J. Effect of combined hydrocortisone, ascorbic acid and thiamine for patients with sepsis and septic shock: a systematic review and meta-analysis. *Shock* 2021;56(6):880–9.
- [186] Ge Z, Huang J, Liu Y, Xiang J, Gao Y, Walline JH, et al. Thiamine combined with vitamin C in sepsis or septic shock: a systematic review and meta-analysis. *Eur J Emerg Med* 2021;28(3):189–95.
- [187] Fujii T, Salanti G, Belletti A, Bellomo R, Carr A, Furukawa TA, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis. *Intensive Care Med* 2022;48(1):16–24.
- [188] Renqi Yao YZ, Yu Yue, Li Zhixuan, Wang Lixue, Zheng Liyu, Li Jiangyan, et al. Combination therapy of thiamine, vitamin C and hydrocortisone in treating patients with sepsis and septic shock: a meta-analysis and trial sequential analysis. *Burns Trauma* 2021;9.
- [189] Iglesias J, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES trial. *Chest* 2020;158(1):164–73.
- [190] Chang P, Liao Y, Guan J, Guo Y, Zhao M, Hu J, et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. *Chest* 2020;158(1):174–82.
- [191] Hwang SY, Ryoo SM, Park JE, Jo YH, Jang DH, Suh GJ, et al. Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. *Intensive Care Med* 2020;46(11):2015–25.
- [192] Moskowitz A, Huang DT, Hou PC, Gong J, Doshi PB, Grossestreuer AV, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. *Jama* 2020;324(7):642–50.
- [193] Wani SJ, Mufti SA, Jan RA, Shah SU, Qadri SM, Khan UH, et al. Combination of vitamin C, thiamine and hydrocortisone added to standard treatment in the management of sepsis: results from an open label randomised controlled clinical trial and a review of the literature. *Infect Dis (Lond)* 2020;52(4):271–8.
- [194] Mohamed ZU, Prasanna P, Moni M, Edathadathil F, Prasanna P, Menon A, et al. Vitamin C therapy for routine care in septic shock (ViCTOR) trial: effect of intravenous vitamin C, thiamine, and hydrocortisone administration on inpatient mortality among patients with septic shock. *Indian J Crit Care Med* 2020;24(8):653–61.
- [195] Sevransky JE, Rothman RE, Hager DN, Bernard GR, Brown SM, Buchman TG, et al. Effect of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in patients with sepsis: the VICTAS randomized clinical trial. *Jama* 2021;325(8):742–50.

- [196] Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF. Nitroglycerin in septic shock after intravascular volume resuscitation. *Lancet* 2002;360(9343):1395–6.
- [197] Boerma EC, Koopmans M, Konijn A, Kaiferova K, Bakker AJ, van Roon EN, et al. Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized placebo controlled trial. *Crit Care Med* 2010;38(1):93–100.
- [198] Lima A, van Genderen ME, van Bommel J, Klijn E, Janssen T, Bakker J. Nitroglycerin reverts clinical manifestations of poor peripheral perfusion in patients with circulatory shock. *Crit Care* 2014;18(3):R126.
- [199] Trzeciak S, Glaspey LJ, Dellinger RP, Durflinger P, Anderson K, Dezfulian C, et al. Randomized controlled trial of inhaled nitric oxide for the treatment of microcirculatory dysfunction in patients with sepsis*. *Crit Care Med* 2014;42(12):2482–92.
- [200] Johannes T, Ince C, Klingel K, Unertl KE, Mik EG. Iloprost preserves renal oxygenation and restores kidney function in endotoxemia-related acute renal failure in the rat. *Crit Care Med* 2009;37(4):1423–32.
- [201] Dépret F, Sitbon A, Soussi S, De Tymowski C, Blet A, Fratani A, et al. Intravenous iloprost to recruit the microcirculation in septic shock patients? *Intensive Care Med* 2018;44(1):121–2.